label, wherein the conjugate is a chemical conjugate, fusion protein or conjugate formed by indirect binding by a positively charged polymer, chimeric antibody or streptavidin.

14. (amended) [The] A conjugate of [claim 13 wherein the conjugate is formed with] an agent binding selectively to endothelial protein C receptor (EPCR) selected from the group consisting of an antibody to EPCR, or a fragment or recombinant molecule based [thereon] of the antibody to EPCR, binding to EPCR, and a molecule to be delivered to a large vessel endothelial cell wherein the molecule is not a diagnostic label, wherein the conjugate is a chemical conjugate, fusion protein or conjugate formed by indirect binding by a positively charged polymer, chimeric antibody or streptavidin.

Remarks

The claimed method is directed to selectively delivering molecules to the nucleus of endothelial cells of the large vessels, by administering a conjugate of an agent binding selectively to endothelial protein C receptor (EPCR) and the molecule to be delivered to large vessel endothelial cells. The conjugate binds to the receptor, the conjugate is endocytosed, and the conjugate thereby delivers the molecule to the cytoplasm or to the nucleus of the large vessel endothelial cells (see claim 1 as originally filed and Examples in specification). The conjugate may be delivered by directly contacting the endothelial cells of large vessels with the conjugate or by catherization within blood vessels formed by the endothelial cells (page 10, lines 15-18). The conjugate may be administered to an individual in need of treatment or diagnosis (page 9, lines 22-26).

The conjugate includes (1) an agent binding to endothelial protein C receptor (EPCR), protein C, activated protein C, antibodies reactive with EPCR, or fragments of protein C,

activated protein C, or antibodies reactive with EPCR which bind to EPCR, and (2) a molecule to be delivered to a large vessel endothelial cell, wherein the molecule is not a diagnostic label (page 4, lines 8-11). The conjugate may be a chemical conjugate, fusion protein or conjugate formed by indirect binding by a positively charged polymer, chimeric antibody or streptavidin (page 2, lines 12-17). The conjugate may also be formed as a recombinant molecule based upon an antibody to EPCR (page 2, line 16). The molecule may be a gene or a cDNA controlled by a promoter expressed in the nucleus of an endothelial cell, a drug other than nucleic acids and proteins (page 6, line 26), a protein or a transcription factor (page 7, lines 16-17). The conjugate may comprise a chimeric antibody which binds to EPCR and to the molecule to be delivered (page 8, lines 15-17). Localization of the conjugate within the endothelial cell (i.e. the nucleus or the cytoplasm) is dependent upon this agent. For example, molecules conjugated to Activated Protein C, or antibodies, will be transported to the nucleus. Molecules conjugated to Protein C will be transported to the cytoplasm.

The molecule is coupled to the EPCR binding agent. Coupling means are well established in the art and include covalent or ionic interactions; chemical coupling, for example, *via* succinic anhydride; chimeric proteins or protein fusions. Indirect binding may be accomplished *via* an intermediate molecule like streptavidin or biotin, or via a positively charged polymer like lysine, pyrrole, or chitosan.

Rejections Under 35 U.S.C. § 112, first paragraph

Claims 1 and 12 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled for a method of treatment. This rejection is respectfully traversed.

The examiner states at page 3, "At best the instant specification disclose the selectively delivering molecules of interest to the nucleus of endothelial cells of the large vessels by administering a conjugate of an agent that bind selectively to the EPCR."

Claim 1 reads:

1. A method for selectively delivering molecules to the nucleus of endothelial cells of the large vessels, comprising

administering a conjugate of an agent binding selectively to endothelial protein C receptor (EPCR) and the molecule to be delivered to large vessel endothelial cells, wherein the molecules are delivered to the nucleus of the large vessel endothelial cells.

Claim 12 reads:

12. The method of claim 1 wherein the conjugate is administered directly to the cells of to an individual in need of treatment or diagnosis.

Nowhere does either claim recite that the method results in the treatment of any and all diseases or disorders in an individual. In fact, claim 1 does not require treatment at all. Claim 12 recites only that the individual is in need of treatment or diagnosis.

i. The Legal Standard.

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*See, e.g., Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v.*

Telectronics, Inc., 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

ii. Factual Analysis of Claims 1 and 12 under U.S.C. § 112, first paragraph.

The pending method claims are directed to selectively delivering molecules to the nucleus of endothelial cells. The specification is clearly enabled for the *delivery* of the claimed

molecules (conjugates of an agent selectively binding to endothelial protein C receptor and the molecule to be delivered). The applicants have provided Examples, that when taken in combination with the state of the art at the time of filing the present application, clearly enable claim 12 as to a method of diagnosis. Example 3 and Figure 1 illustrate the efficiency of reporter gene transfer to the nucleus of endothelial cells. The reporter gene is complexed with anti-EPCR monoclonal antibodies *via* poly-L-lysine and targeted to the endothelial cell receptor. Once bound to the receptor, the complex is internalized by the cell and transported to the nucleus for expression of the reporter gene. Figure 1 shows a consistently higher level of reporter gene expression in cells that were transfected with reporter gene DNA complexed with anti-EPCR monoclonal antibodies as compared to cells being targeted *via* non-specific monoclonal antibodies (an approximately 25-fold increase over the control in one sample). Given the positive charge of poly-L-lysine, one of ordinary skill in the art would reasonably expect and realize, in view of Example 3, that nucleic acids (negatively charged) readily form complexes with the poly-L-lysine coupled to the EPCR-monoclonal antibodies. Once bound by the endothelial cell receptor, these complexes are efficiently taken up by the endothelial cells harboring the receptor, transported to the nucleus, and the genes within the complex expressed.

Claim 12 is directed to the administration of the conjugate to cells of an individual in need of treatment or diagnosis (claim 12). The applicants have submitted data in the form of a reference by Baumgartner *et al.* (*Circulation*, March 31, 1998; see After Final amendment and response mailed on February 4, 2002), to show the state of the art with regard to treating endothelial cells at the time of filing the present application, August 1998. Baumgartner *et al.* demonstrates therapeutic intramuscular gene transfer to endothelial cells in need of treatment

using plasmid DNA encoding an endothelial cell mitogen. Baumgartner explicitly teaches successful gene therapy to endothelial cells. Baumgartner presents results from a phase 1 trial, "unanimously approved by the Recombinant DNA Advisory Committee and the U.S. Food and Drug Administration" and used to study new chemotherapeutic agents administered to human subjects. The data presented shows gene expression *at the protein level* as a transient peak of gene product in the systemic circulation one to three weeks after gene transfer (see Figure 1, and description at page 1116 of Baumgartner).

The applicants respectfully submit that the predictability, or lack thereof, in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention. What is known in the art provides evidence as to the question of predictability. *In re Marzocchi*, 439 F.2d 220, 223-224, 169 USPQ 367, 369-370 (CCPA 1971). As taught by Baumgartner *et al.*, the transfer of naked DNA *to endothelial cell* wherein the DNA is stably expressed, had been accomplished with success. The Examiner has continually argued that there is no conclusive evidence of successful treatment of human disease using gene therapy. The Examiner appears to have not even considered the data presented by Baumgartner *et al.*, wherein nonhealing ischemic ulcers and/or rest pain due to peripheral arterial disease are healed or markedly improved, including successful limb salvage in three patients using gene therapy directed to endothelial cells.

In view of the specification, the Examples therein, and the references that have been previously submitted (in particular, the Baumgartner *et. al.* reference), one of ordinary skill in the art would have reasonably expected that the claimed method, using molecules conjugated to agents that selectively bind to EPCR, could be effectively used *for the delivery* of nucleic acid to

endothelial cells in need of treatment. The examiner has provided no evidence that one could not practice the claimed method. The examiner has instead relied on conclusory statements without putting forth specific reasons describing why the claims are not enabled by the specification. The patent examiner cannot just assert that the application is not enabled. As stated in In re Marzocchi at 439 F.2d 220 (CCPA 1971:

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made [, enablement under § 112, first paragraph], to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the Applicants to go to the trouble and expense of supporting his presumptively accurate disclosure.
>
> *Id.* at 224.

As an illustration of the examiner's burden, in *Ex parte Goeddel*, 5 U.S.P.Q.2d 1449 (1985), the Board of Patent Appeals overturned an examiner's rejection based on lack of enablement. The invention at issue claimed therapeutically active fraction of a polypeptide consisting essentially of the amino acid sequence of a mature human leukocyte interferon. Although the examiner cited *Jackson* for the proposition that the art was uncertain, the Board found that, where "applicants in a comprehensive and detailed disclosure have set forth the manner by which the claimed leukocyte interferons may be obtained," one "skilled in this art palpably would have no difficulty following applicants' instructions in order to realize the claimed product staring with known and available precursors." Accordingly, the vague citation to

Jackson did not "rebut applicants' extensive and well reasoned arguments that the disclosure in *this* case is adequate . . . . Mere broad generalizations and allegations are insufficient for holding of non-enablement."

In this case, the examiner has not even bothered to respond to the evidence and why it is not considered sufficient to overcome all of the rejections, noting only that "the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims" This is not the legal standard, however. All applicants must establish is that one can practice the claimed method. This they have done, not just made assertions.

Rejections under 35 U.S.C. 112, second paragraph

Claims 13 and 14 were rejected under 35 U.S.C. 112, second paragraph, as indefinite with respect to the phrase "fragments thereof" and "recombinant molecule based thereon", respectively. The claims have been amended to clarify the claimed subject matter.

Rejections Under 35 U.S.C. § 102

Claims 13, 15, 19, and 20 were rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,225,537 to Foster,e t al. ("Foster") or U.S. Patent No. 5,571,786 to Eibl, et al. ("Eibl").

i. The Legal Standard.

For a rejection of claims to be properly founded under 35 USC §102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech Inc v Monoclonal Antibodies Inc*, 231 USPQ 81 (Fed. Cir. 1986), *cert. denied*, 480 US 947 (1987);

Scripps Clinic & Research Found v Genentech Inc, 18 USPQ2d 1001 (Fed. Cir. 1991). The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. . . *There must be no difference* between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention. (Emphasis added)

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps, Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to practice the invention. The Federal Circuit held that "a §102(b) reference must sufficiently describe the claimed invention to have placed the public in possession of it. . . [E]ven if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling." *Paperless Accounting Inc v Bay Area Rapid Transit Sys.*, 231 USPQ 649, 653 (Fed. Cir. 1986) (citations omitted).

ii. The Prior Art.

Foster

Foster describes a fusion of:

PAP-I and protein C DNA.

Claim 13 defines a conjugate of

(a) an agent binding selectively to endothelial protein C receptor (EPCR) selected from the group consisting of protein C, activated protein C, antibodies reactive with EPCR and fragments of the antibodies reactive with EPCR binding to EPCR, and

(b) a molecule selected from the group consisting of nucleic acids, proteins, drugs and diagnostic agents to be delivered to a large vessel endothelial cell, wherein the molecule is not a diagnostic label,

(c) wherein the conjugate is a chemical conjugate, fusion protein or conjugate formed by indirect binding by a positively charged polymer, chimeric antibody or streptavidin.

PAP-I could be construed to be a molecule to be delivered, for some unknown purpose.

However, the protein C fusion of Foster is only a fragment of the protein C, not the full protein, and therefore not within the scope of the agents selectively binding to EPCR.

Therefore, Foster does not anticipate claims 13, 15, 20 or 22.

Eibl

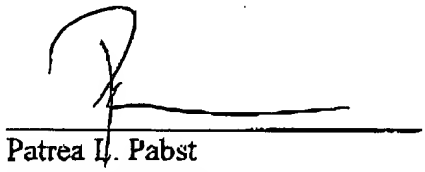
Eibl describes the binding of activated protein C to thrombin coupled to CNBr-Sepharose in a method for purifying the activated protein C. One could hardly construe thrombin coupled to Sepharose as "a molecule to be delivered to a large vessel endothelial cell, wherein the molecule is not a diagnostic label". First, thrombin coupled to Sepharose is not "a molecule" but

a complex of a protein coupled by cyanogens bromide coupling to a large polysaccharide. Second, it is not suitable for delivery to a large vessel endothelial cell. However, to make this even more clear, the claim has been amended to define the molecule to be delivered as selected from the group consisting of "nucleic acids, proteins, drugs and diagnostic agents". This is supported in the specification at page 6, lines 25-26, and clearly excludes a protein coupled to a chromatography column material as described by Eible.

Claims 13, 15, 20, and 22-23 are therefore clearly distinguished from Eible.

Allowance of all claims 1-25 is earnestly solicited.

Respectfully submitted,

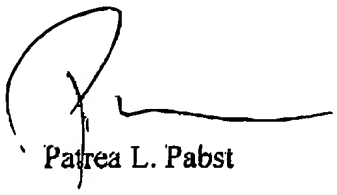


Patrea L. Pabst
Reg. No. 31,284

Date: December 11, 2002
HOLLAND & KNIGHT LLP
One Atlantic Center, Suite 2000
1201 West Peachtree Street
Atlanta, Georgia 30309-3400
(404) 817-8473
(404) 817-8588 (fax)

Certificate of Facsimile Transmission

I hereby certify that this Amendment along with any paper referred to as being attached or enclosed, is being facsimile transmitted to the Assistant Commissioner of Patents at the U.S. Patent Office on December 11, 2002.



Patrea L. Pabst